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Effects of Oral Crystalline Cyanocobalamin 1000 µg/d in the Treatment of Pernicious Anemia: An Open-Label, Prospective Study in Ten Patients

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ABSTRACT

Background: Standard treatment of cobalamin (vitamin B_{12}) deficiency involves regular (1000 µg/mo) IM cyanocobalamin administration. It has been suggested that high-dose (>2000 µg/d) oral cyanocobalamin may be effective in patients with pernicious anemia.

Objective: The aim of this study was to assess the efficacy and tolerability of oral crystalline cyanocobalamin 1000 µg/d in patients with cobalamin deficiency related to established pernicious anemia.

Methods: This open-label, prospective study was conducted at Strasbourg University Hospital, Strasbourg, France. Patients aged ≥18 years with well-documented cobalamin deficiency related to pernicious anemia were enrolled. Patients received crystalline cyanocobalamin 1000 µg QD PO (capsule) for at least 3 months. Serum cobalamin, folate, iron, and homocysteine concentrations were measured, and a complete blood count was obtained, before (month 0; baseline) and after treatment.

Results: Ten patients (7 women, 3 men; mean [SD] age, 72.1 [15.5] years) entered the study. After 3 months of treatment, serum cobalamin concentration increased in all 9 patients in whom it was measured (mean [SD] increase, 117.4 [30.8] pg/mL; $P < 0.001$ vs baseline). Serum cobalamin concentrations were normalized (>200 pg/mL) in 6 patients. The serum cobalamin concentration was unavailable in 1 patient because of technical problems. Eight patients had increased hemoglobin concentrations (mean [SD] increase, 2.5 [2.4] g/dL; $P < 0.01$ vs baseline). All 10 patients had decreased mean erythrocyte corpuscular volumes (mean [SD] decrease, 10.4 [6.2] fL; $P < 0.003$ vs baseline). Four patients received concomitant blood transfusions or folate and iron supplementation. Three patients experienced clinical improvement in paresthesia, reflex abolition, or combined medullary sclerosis (each, 1 patient).

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Conclusion: The results of this small study in patients with cobalamin deficiency related to pernicious anemia suggest that oral crystalline cyanocobalamin 1000 µg/d may be an effective treatment. (*Curr Ther Res Clin Exp.* 2005;66: 13–22) Copyright © 2005 Excerpta Medica, Inc.

Key words: cobalamin deficiency, pernicious anemia, oral cyanocobalamin treatment.

INTRODUCTION

Approximately 15% of people aged >60 years in the United States are thought to have undiagnosed cobalamin (vitamin B_{12}) deficiency.[1] The most common causes, particularly in elderly (aged ≥65 years) patients, are cobalamin malabsorption from food and pernicious anemia (Addison-Biermer anemia).[2,3] Pernicious anemia is a chronic illness caused by impaired absorption of cobalamin due to intrinsic factor deficiency.[3,4] Two mechanisms are responsible. First, the progressive destruction and eventual loss of parietal cells from the gastric mucosa lead to failure of intrinsic factor production.[4] Second, blocking autoantibodies in the bile can bind to the cobalamin binding site of intrinsic factor, thereby preventing the formation of the cobalamin–intrinsic factor complex.[4] Standard treatment of cobalamin deficiency involves regular (1000 µg/mo) IM cyanocobalamin injections. It has been suggested that high-dose (>2000 µg/d) oral cyanocobalamin therapy may be effective for cobalamin deficiency,[5] but rarely in established pernicious anemia. However, the utility of the 1000-µg/d dose was previously documented in 3 patients at Strasbourg University Hospital, Strasbourg, France.[6,7]

Based on a MEDLINE search (key terms: *cobalamin deficiency and treatment* and *vitamin B_{12} deficiency and treatment*; years: 1966–2004), currently, only case reports[6,7] and studies with poorly determined or undetermined causes of cobalamin deficiency[8,9] have been published. Thus, we studied the efficacy and tolerability of oral crystalline cyanocobalamin 1000 µg/d in patients with cobalamin deficiency related to established pernicious anemia.

PATIENTS AND METHODS

Patient Selection

Patients aged ≥18 years were recruited from the Departments of Internal Medicine, Diabetes and Metabolic Disorders, Hematology, Nutrition, and Geriatrics, Strasbourg University Hospital, between February 1998 and September 2003. Patients underwent a clinical examination, including the Schilling test,[10] to establish a diagnosis of pernicious anemia. Urine samples were then collected over 24 hours (from day 2 to day 3), and the percentage of labeled cyanocobalamin was determined (<6%). To be included in this open-label, prospective study, patients met the following criteria: (1) serum cobalamin concentration <200 pg/mL confirmed on 2 serum samples or in association with a homocysteine concentration >13 µmol/L[11,12] and (2) evidence

of serum antibodies to intrinsic factor[4] that established the diagnosis of pernicious anemia.[11,12] The Schilling test was performed as follows: patients were administered cyanocobalamin 1000 µg IM on day 1, and 1000 µg cyanocobalamin free of ^{57}CO-cobalamin PO on day 2.

Patients were excluded if they were unable to follow a physician's directives or take oral medication, had a severe associated condition (eg, cardiac or respiratory failure, liver failure, inflammatory bowel disease), or had a history of malignancy or hypersensitivity to cobalamin. Folate and iron deficiencies were not exclusion criteria. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study.

All eligible patients provided verbal informed consent to participate. An institutional review board (the Cobalamin Deficiency Study Group at Strasbourg University Hospital) approved the study protocol.

Study Procedures

Crystalline cyanocobalamin* 1000 µg QD PO (capsule) was self-administered for at least 3 months. Serum samples were obtained before (month 0; baseline) and after 3 months of treatment. Serum cobalamin, folate, iron, and homocysteine concentrations were measured, and a complete blood count was obtained.

The primary efficacy end point was normalization of serum cobalamin concentration (>200 pg/mL). Secondary end points involved reversal of blood count abnormalities (hemoglobin [Hb] concentration, >12 g/dL; mean erythrocyte corpuscular volume [ECV], <100 fL; platelet count, >150 × 10^9 cells/L). Improvement in clinical findings (including neuropsychiatric status) was not considered an end point, given the difficulty of correlating clinical features with cobalamin deficiency (particularly in elderly patients) and with the severity of cobalamin deficiency.[3,13]

Tolerability was assessed by recording adverse effects identified using patient interview and laboratory analysis, including hematology, biochemistry, and liver and kidney function tests.

Laboratory Analysis

An automated Coulter counter (Technikon H1, Bayer HealthCare, Diagnostics Division, Tarrytown, New York) was used to measure hematologic variables. Serum cobalamin and folate concentrations were determined by enzyme immunoassay using a commercially available kit (Abbott Diagnostics, Rungis, France). The total serum homocysteine level was measured using capillary gas chromatography–mass spectrometry. Serum anti-intrinsic factor antibodies were determined by enzyme-linked immunosorbent assay using a commercially available kit (Bayer HealthCare, Diagnostics Division).

*Trademark: Vitamine B12® (Mille Delagrange Synthelabo, Meudon-la-Forêt, France, or Aguettan, Lyon, France).

Statistical Analysis

Pretreatment and posttreatment values were compared using the Student *t* test for paired data. $P < 0.05$ was considered statistically significant. Data are expressed as mean (SD). StatView version 4.0 (SAS Institute Inc., Cary, North Carolina) was used for statistical analysis.

RESULTS

Of the 32 patients diagnosed with pernicious anemia during the recruitment period, 22 were excluded for the following reasons: concomitant life-threatening conditions (8 patients); inability to follow physician's directives (5); refusal to participate (5); and residing outside the immediate geographic area of Strasbourg University Hospital, thereby impeding adequate follow-up (4). The remaining 10 patients entered the study, 3 of whom had an absolute contraindication to IM cyanocobalamin therapy because they were receiving anticoagulant treatment.

Patient Characteristics

All 10 patients (7 women, 3 men; mean [SD] age, 72.1 [15.5] years) were white (**Table I**). All patients met the criteria for pernicious anemia with evidence of intrinsic factor antibodies. The Schilling test showed malabsorption with crystalline ^{57}CO-cobalamin in 3 patients. Immune gastric atrophy was observed in all 4 of the patients who underwent upper gastrointestinal endoscopy. All 10 patients had documented cobalamin deficiency. The mean (SD) pretreatment serum cobalamin concentration was 106.5 (30.5) pg/mL; homocysteine, 18.2 (3.4) µmol/L; and Hb, 9.2 (2.7) g/dL. Mean folate levels and iron status were normal except in 3 patients, who were treated with folate and iron supplementation. Two patients had diabetes mellitus, 4 had hypertension, and 1 had moderate renal failure.

Treatment Response

After 3 months of treatment, serum cobalamin concentrations were measured in 9 patients, all of whom had increased concentrations compared with baseline (mean [SD] increase, 117.4 [30.8] pg/mL; $P < 0.001$). Serum cobalamin concentrations were normalized in 6 patients (**Table II**). Posttherapeutic serum cobalamin concentration was not available in 1 patient because of technical problems. Eight patients had increased Hb concentrations (mean [SD] increase, 2.5 [2.4] g/dL; $P < 0.01$), and Hb concentrations were normalized in 6 patients.

Four patients received concomitant blood transfusions or folate and iron supplementation. If 2 patients were excluded from this analysis because they received blood transfusions, the mean increase in Hb concentration was 1.5 (2.0) g/dL ($P < 0.043$). All 10 patients had decreased mean ECV (mean [SD] decrease, 10.4 [6.2] fL; $P < 0.003$ vs baseline), and the mean value was normalized

Table I. Baseline demographic and clinical characteristics of the study patients (N = 10).

Patient No.	Sex/ Age, y	Symptoms	Hematologic Data	Serum Cobalamin Concentration, pg/mL	Serum Homocysteine Concentration, µmol/L
1	F/81	Asthenia, reflex loss, lower limb edema	WBC = 3.8×10^9 cells/L; Hb = 6.8 g/dL; ECV = 111 fL; PC = 160×10^9 cells/L (anemia,* leukopenia†)	97	22
2	F/78	Asthenia, memory loss	WBC = 5.7×10^9 cells/L; Hb = 7.4 g/dL; ECV = 109 fL; PC = 147×10^9 cells/L (anemia*)	56	18
3	F/71	Reflex loss	WBC = 8.2×10^9 cells/L; Hb = 11.7 g/dL; ECV = 95 fL; PC = 189×10^9 cells/L (anemia*)	142	17
4	F/67	Jaundice (hemolysis), reflex loss	WBC = 4.5×10^9 cells/L; Hb = 5.2 g/dL; ECV = 114 fL; PC = 49×10^9 cells/L; evidence of schistocytes (thrombotic microangiopathy syndrome‡)	120	19
5	M/69	None	WBC = 4.5×10^9 cells/L; Hb = 8 g/dL; ECV = 112 fL; PC = 70×10^9 cells/L; evidence of schistocytes (thrombotic microangiopathy syndrome‡)	100	ND
6	F/80	Combined medullary sclerosis	WBC = 6.4×10^9 cells/L; Hb = 10 g/dL; ECV = 102 fL; PC = 110×10^9 cells/L; evidence of rare schistocytes (thrombotic microangiopathy syndrome‡)	60	ND
7	M/88	Dementia	WBC = 5.9×10^9 cells/L; Hb = 7.7 g/dL; ECV = 93 fL; PC = 268×10^9 cells/L (anemia*)	110	24
8	F/82	None	WBC = 7.1×10^9 cells/L; Hb = 9.6 g/dL; ECV = 98 fL; PC = 163×10^9 cells/L (anemia*)	110	14
9	M/73	None	WBC = 5.7×10^9 cells/L; Hb = 13.1 g/dL; ECV = 106 fL; PC = 211×10^9 cells/L (isolated macrocytosis)	120	17
10	F/32	Paresthesia	WBC = 7.1×10^9 cells/L; Hb = 12.9 g/dL; ECV = 92 fL; PC = 169×10^9 cells/L (no abnormalities)	150	15

F = female; WBC = white blood cell count; Hb = hemoglobin concentration; ECV = mean erythrocyte corpuscular volume; PC = platelet count; M = male; ND = not determined.

*Anemia = Hb concentration <12 g/dL.

†Leukopenia = WBC <4×10^9 cells/L.

‡Thrombocytopenia = PC <100×10^9 cells/L. Thrombotic microangiopathy syndrome involves anemia, thrombocytopenia, and evidence of schistocytes.

Table II. Laboratory values before (month 0; baseline) and after 3 months of treatment with oral crystalline cyanocobalamin 1000 µg/d.

Patient No.	Serum Cobalamin Concentration, pg/mL		Hb, g/dL		ECV, fL	
	Before	After	Before	After	Before	After
1	97	230	6.8	12.3*	111	99*
2	56	180	7.4	12.1†	109	86†
3	142	270	11.7	12.0	95	91
4	120	260‡	5.2	11.7‡	114	98‡
5	100	190	8.0	9.4	112	102
6	60	120	10.0	12.8*	102	87*
7	110	ND	7.7	10.2*	93	85*
8	110	202	9.6	10.7	98	94
9	120	250	13.1	12.9	106	98
10	150	310	12.9	12.8	92	88
Mean (SD)	106.5 (30.5)	223.6 (56.9)§	9.2 (2.7)	11.7 (1.2)‖	103.2 (8.3)	92.8 (6.2)¶

Hb = hemoglobin concentration; ECV = mean erythrocyte corpuscular volume; ND = not determined.
*This patient was treated with folate and iron supplementation.
†This patient was initially treated with a blood transfusion (2 U).
‡This patient was initially treated with a blood transfusion (4 U).
§$P < 0.001$ versus baseline.
‖$P < 0.01$ versus baseline.
¶$P < 0.043$ versus baseline.

in 9 patients (**Table II**). Platelet counts normalized in all 3 patients with thrombocytopenia. Serum homocysteine levels were measured in 3 patients, all of whom had decreased levels compared with baseline (mean [SD] decrease, 1.2 [0.7] µmol/L; $P = 0.047$). Three patients experienced clinical improvements in paresthesia, reflex abolition, or combined medullary sclerosis (each, 1 patient).

Compliance and Tolerability

All 10 patients reported being fully compliant with the study medication, although compliance was not systematically studied. One patient experienced transient localized urticarial eruption after 2 months of cyanocobalamin therapy. During the eruption, the patient also was receiving ampicillin for a sore throat.

DISCUSSION

The results of this open-label study suggest that patients with established cobalamin deficiency related to pernicious anemia generally benefit from crystalline cyanocobalamin 1000 µg QD PO. These results may be of particular interest in patients with contraindications to IM cyanocobalamin (eg, concomitant anticoagulant therapy).[14]

All patients had well-documented pernicious anemia with evidence of intrinsic factor antibodies, which had a specificity >98% (sensitivity, >50%),[3,15] and cobalamin deficiency.[11,12,16,17] Nine of the 10 patients had blood abnormalities: anemia, macrocytosis, thrombocytopenia, or thrombotic microangiopathy syndrome (indicated by evidence of schistocytes), all of which are late findings in cobalamin deficiency.[14,18,19]

All patients who were tested showed improvements in serum cobalamin concentrations and hematologic abnormalities. Serum cobalamin concentrations were normalized in 6 patients. In 1 patient, follow-up cobalamin concentrations were not measured because of technical problems; this patient had a major improvement in Hb concentration. Two patients were given blood transfusions (2 and 4 U), which provided 1.25 and 2.50 g, respectively, of cobalamin. All anemic patients had improvements in their Hb concentration, even in the case of severe anemia (Hb concentration, <8 g/dL). In 4 patients, these improvements were also due to additional therapy: blood transfusion and folate and iron supplementation. We could not rule out the possibility that these additional therapies provided a false-positive response of oral cyanocobalamin therapy. Three patients also received IM cyanocobalamin for the Schilling test, but we have previously demonstrated that this does not interfere with increased cobalamin concentrations.[20]

These results are consistent with those observed in larger studies that used enteral cyanocobalamin.[8,20–23] However, the larger studies used higher doses of cyanocobalamin and/or included patients without a well-determined cause of cobalamin deficiency. In a randomized trial of 18 patients that included patients with pernicious anemia,[8] 4 months of treatment with oral cyanocobalamin 2000 µg/d led to improvements in hematocrit, mean ECV, and cobalamin concentration in half of the treated patients. In another randomized study, Bolaman et al[9] reported similar effectiveness of oral (1000 µg/d) and IM (1000 µg/mo) cyanocobalamin therapy in 60 patients, including 8 patients with pernicious anemia. After 3 months of treatment, they reported significant improvements in all hematologic parameters and cobalamin concentrations. Kondo[22] reported similar benefits with massive doses (>10,000 µg/wk) of oral cyanocobalamin. These results are also consistent with several observations reported previously.[6,7] In these patients, cobalamin deficiency related to pernicious anemia was resolved with oral cyanocobalamin 1000 µg/d.[6,7]

Only 3 patients in the present study reported clinical improvement, although 1 patient had total regression of combined medullary sclerosis. The results of the present study are similar to those from the study by Kuzminski et al,[8] in which neurologic symptoms (eg, paresthesias) improved in only 4 of 18 patients. Bolaman et al[9] reported neurologic improvement in 7 of 9 symptomatic patients. In our study, the lack of clinical improvement may have been related to the short duration of treatment and follow-up.[24,25] Moreover, several neurologic manifestations of cyanocobalamin therapy were nonregressive despite a well-documented, effective therapy.[26,27] Some of the clinical findings in the present

study may also have been the result of age (mean [SD] age, 72.1 [15.5] years) or other underlying disorders (eg, diabetes).

The results of the present study support those from a study of the usefulness of oral crystalline cyanocobalamin in food-cobalamin malabsorption,[25] a disorder characterized by normal absorption of free cobalamin (malabsorption of bound cobalamin).[27,28] These results (the effectiveness of oral cyanocobalamin therapy) may be related to the existence of a mechanism of simple diffusion, independent of intrinsic factor and cubulin, that permits absorption of a variable percentage of oral cyanocobalamin,[3,5,15,29] even in the case of intrinsic factor deficiency (the failure of intrinsic factor production and the presence of blocking intrinsic factor antibodies), as in pernicious anemia.[3,4] Studies in volunteers have demonstrated that ~1% to 5% of a large dose of oral cyanocobalamin is absorbed via this mechanism.[3,15] Although results suggest that oral crystalline cyanocobalamin may be effective for the treatment of pernicious anemia,[6–9,21–23] the ideal dose remains to be determined.[5,30,31] The patients in the present study received 1000 µg/d of crystalline cyanocobalamin, with good efficacy. Kuzminski et al[8] studied a higher dose of cyanocobalamin (2000 µg/d), with no increased benefit. Three of the patients in the present study had posttreatment cobalamin concentrations <200 pg/mL. One explanation may be the use of low-dose cyanocobalamin (perhaps 2000 µg/d may be more effective) or poor compliance with oral therapy, which was not systematically assessed in this study.

This study was limited by its small sample size, relatively short treatment period (at least 3 months), the absence of randomization of a control group, and by the fact that 4 patients received concomitant blood transfusions or folate and iron supplementation. Nonetheless, given the apparent effectiveness of oral therapy and its possible benefits, including better compliance compared with IM treatment, or interest in patients who had an absolute contraindication for IM cyanocobalamin (eg, concomitant anticoagulation therapy), further studies with larger sample sizes that use different cyanocobalamin doses are warranted.

CONCLUSION

The results of this small study in patients with cobalamin deficiency related to pernicious anemia suggest that oral crystalline cyanocobalamin 1000 µg/d may be an effective treatment.

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